IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Howard M. Dintzis and Renee Z. Dintzis	Art Unit	: to be assigned
		Examiner	: to be assigned
Serial No.	: to be assigned		
Filed	: January 9, 2001		
Title	: THERAPEUTIC SUPPRESSION OF SPECIFIC IMMUNE RESPONSES BY ADMINISTRATION OF OLIGOMERIC FORMS OF ANTIGEN OF CONTROLLED CHEMISTRY		

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination of this continuation application, Applicants respectfully request entry of the amendments and consideration of the remarks set forth herein.

This preliminary amendment is being filed together the continuation's transmittal papers, specification and other documents.

AMENDMENT

Please amend the above-captioned application as follows:

In The Specification:

On page 1, delete lines 5 to 16, and insert therefor:

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL558601890US

I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

January 9, 2001
Date of Deposit

Signature

Richard Donovan
Typed or Printed Name of Person Signing Certificate

--This application is a continuation of U.S. Patent Applications Serial No. ("USSN") 08/440,331, filed May 12, 1995, now pending and USSN 08/440,322, filed May 12, 1995, now pending, which are continuations of USSN 08/391,267, filed February 21, 1995, issued as U.S. Patent No. 6,022,544, on February 8, 2000, which is a continuation of USSN 07/808,797, filed Dec. 17, 1991 (now abandoned) which is a continuation-in-part of USSN 07/628,858, filed Dec. 17, 1990 (now abandoned), which is a continuation-in-part of USSN 07/354,710, filed May 22, 1989 (now abandoned), which is a continuation-in-part of USSN 07/248,293, filed Sep. 21, 1988, issued as U.S. Patent No. 5,126,131, on June 30, 1992, which is a continuation of USSN 06/869,808, filed May 29, 1986 (now abandoned), which is a continuation of USSN 06/460,266, filed Jan. 24, 1983 (now abandoned). Each of the aforementioned applications and patents are explicitly incorporated herein by reference in their entirety and for all purposes.--

On page 61, line 4, after "Lupus 7'"., insert --SEQ ID NO:1--.

On page 61, line 5, after "Lupus 2'.", insert --SEQ ID NO:2--.

On page 61, line 7, after "3'.", insert --SEQ ID NO:3--.

On page 61, line 9, after "4'.", insert --SEQ ID NO:4--.

On page 61, line 11, after "5'.", insert --SEQ ID NO:5--.

On page 61, line 12, after "-$CONH_2$", insert --SEQ ID NO:6--.

On page 61, line 14, after "$CONH_2$", insert --SEQ ID NO:7--.

On page 61, line 16, after "$CONH_2$", insert --SEQ ID NO:8--.

On page 61, line 18, after "$CONH_2$", insert --SEQ ID NO:9--.

On page 61, line 20, after "$CONH_2$", insert --SEQ ID NO:10--.

On page 61, line 21, after "$CONH_2$", insert --SEQ ID NO:11--.

On page 61, line 22, after "$CONH_2$", insert --SEQ ID NO:12--.

On page 61, line 24, after "$CONH_2$", insert --SEQ ID NO:13--.

On page 61, line 26, after "COOH", insert --SEQ ID NO:14--.

On page 61, line 28, after "$CONH_2$", insert --SEQ ID NO:15--.

On page 86, line 32, after "$CONH_2$", insert --SEQ ID NO:2--.

On page 87, line 22, after "$CONH_2$", insert --SEQ ID NO:2--.

On page 89, line 24, after "CO_2H", insert --SEQ ID NO:16--.

On page 90, line 24, after "CO_2H", insert --SEQ ID NO:16--.

On page 93, line 6, after "$CONH_2$", insert --SEQ ID NO:17--.

On page 93, line 19, after "$CONH_2$", insert --SEQ ID NO:18--.

On page 93, line 26, after "$CONH_2$", insert --SEQ ID NO:19--.

On page 113, line 26, after "$CONH_2$", insert --SEQ ID NO:19--.

On page 133, line 3, after "leucine-alanine", insert --SEQ ID NO:20--.

On page 133, line 6, after "amide", insert --SEQ ID NO:21--.

On page 140, line 16, after "P-A-K-S-A-P-A-P-K-K-)", insert --SEQ ID NO:22--.

On page 140, line 20, after "NH2)", insert --SEQ ID NO:23--.

In The Claims:

Please cancel claims 1 to 43.

Please add the following new claims:

--44. A method of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, which copies bind to a B cell membrane immunoglobulin receptor specific for the epitope but fail to form an immunon, comprising

(a) providing a non-immunogenic soluble carrier that has been subjected to a preparative sizing technique to remove substantially most high molecular weight non-immunogenic soluble carrier molecules and an epitope molecule of a T-dependent antigen;

(b) coupling two or more of the epitope molecules to the size-fractionated non-immunogenic soluble carrier to yield a conjugate preparation, thereby yielding a non-immunogenic construct which is free of high molecular weight immunostimulatory molecules.

45. The method of claim 44, wherein the epitope comprises a peptide epitope.

46. The method of claim 44, wherein the epitope comprises a carbohydrate epitope.

47. The method of claim 44, wherein the epitope comprises a nucleic acid.

48. The method of claim 47, wherein the nucleic acid comprises a phosphorothioate nucleic acid.

49. The method of claim 44, wherein the epitope comprises a glycolipid epitope.

50. The method of claim 44, wherein the epitope is derived from an allergen.

51. The method of claim 44, wherein the epitope is derived from an autoimmune antigen.

52. The method of claim 44, wherein the non-immunogenic carrier comprises a dextran, a Ficoll, a carboxymethylcellulose, a polyvinyl alcohol, a synthetic polymer of D amino acids or a polyacrylamide.

53. The method of claim 52, wherein the synthetic polymer of D amino acids comprises a poly (D-GLU/D-LYS).

54. The method of claim 44, wherein the non-immunogenic carrier comprises a protein oligomer.

55. The method of claim 54, wherein the protein oligomer comprises an immunoglobulin or albumin.

56. The method of claim 44, wherein after the preparative sizing technique the size-fractionated non-immunogenic carrier has a molecular weight of less than about 100,000 daltons.

57. The method of claim 56, wherein after the preparative sizing technique the size-fractionated non-immunogenic carrier has a molecular weight of less than about 40,000 daltons.

58. The method of claim 57, wherein after the preparative sizing technique the size-fractionated non-immunogenic carrier has a molecular weight of less than about 20,000 daltons.

59. The method of claim 44, wherein the preparative sizing technique comprises size exclusion gel chromatography.

60. The method of claim 44, wherein the preparative sizing technique comprises ultrafiltration.

61. The method of claim 44, wherein the copies of the epitope are bound to the non-immunogenic carrier by a spacer molecule.

62. The method of claim 61, wherein the spacer molecule comprises an epsilon amino caproic acid or a delta amino valeric acid.

63. The method of claim 44, wherein the non-immunogenic construct comprises from about 4 to about 30 copies of the epitope.

64. The method of claim 63, wherein the non-immunogenic construct comprises from about 6 to about 14 copies of the epitope.

65. The method of claim 44, wherein the non-immunogenic construct comprises less than about 20 copies of the epitope.

66. The method of claim 44, wherein the non-immunogenic construct is immunosuppressive when administered in pharmacologically effective amounts.

67. The method of claim 66, wherein the non-immunogenic construct is immunosuppressive to T cells.

68. The method of claim 44, wherein the non-immunogenic construct is tolerogenic when administered in pharmacologically effective amounts.

69. A method of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, wherein construct-bound copies of the epitope are capable of binding to a B cell membrane immunoglobulin receptor specific for the epitope without forming a clustering of B cell membrane-bound receptors, the method comprising

(a) providing a preparation of a non-immunogenic soluble carrier, wherein substantially all high molecular weight non-immunogenic soluble carrier molecules have been removed from the preparation, and an epitope of a T-dependent antigen; and

(b) coupling the two or more copies of the epitope to the non-immunogenic soluble carrier to yield a non-immunogenic epitope-coupled construct.

70. A method of making a non-immunogenic epitope-coupled construct preparation comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, wherein at least two copies of construct-bound epitope are capable of binding to a B cell membrane immunoglobulin receptor specific for the epitope without forming a clustering of B cell membrane-bound receptors, the method comprising

(a) providing a soluble carrier and an epitope of a T-dependent antigen;

(b) coupling the two or more copies of said epitope to the soluble carrier; and,

(c) removing substantially all immunostimulatory molecules from the product of the reaction of step (b) to generate a non-immunogenic epitope-coupled construct preparation.

71. The method of claim 70, wherein the non-immunogenic epitope-coupled construct preparation has a molecular weight of less than about 100,000 daltons.

72. The method of claim 71, wherein the non-immunogenic epitope-coupled construct preparation has a molecular weight of less than about 40,000 daltons.

73. The method of claim 72, wherein the non-immunogenic epitope-coupled construct preparation has a molecular weight of less than about 20,000 daltons.

74. The method of claim 70, wherein substantially all immunostimulatory molecules are removed from the product of the reaction of step (b) by size exclusion gel chromatography.

75. The method of claim 70, wherein substantially all immunostimulatory molecules are removed from the product of the reaction of step (b) by ultrafiltration.

76. The method of claim 70, wherein the epitope comprises a phosphorothioate nucleic acid.

77. The method of claim 70, wherein the epitope is derived from an allergen.

78. The method of claim 70, wherein the epitope is derived from an autoimmune antigen.

79. The method of claim 70, wherein the non-immunogenic carrier comprises a polyvinyl alcohol, a synthetic polymer of D amino acids or a polyacrylamide.

80. The method of claim 70, wherein the copies of the epitope are bound to the carrier by a spacer molecule, wherein the spacer molecule comprises an epsilon amino caproic acid or a delta amino valeric acid.

81. The method of claim 70, wherein the non-immunogenic epitope-coupled construct preparation comprises from about 4 to about 30 copies of the epitope.

82. The method of claim 81, wherein the non-immunogenic epitope-coupled construct preparation comprises from about 6 to about 14 copies of the epitope.

83. The method of claim 70, wherein the non-immunogenic epitope-coupled construct preparation comprises less than about 20 copies of the epitope.

84. The method of claim 70, wherein the non-immunogenic construct is immunosuppressive when administered in pharmacologically effective amounts.

85. The method of claim 70, wherein the non-immunogenic construct is immunosuppressive to T cells.

86. The method of claim 70, wherein the non-immunogenic construct is tolerogenic when administered in pharmacologically effective amounts.

87. A pharmaceutical composition comprising a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, wherein at least two copies of construct-bound epitope are capable of binding to a B cell membrane immunoglobulin receptor specific for the epitope without forming a clustering of B cell membrane-bound receptors.--

REMARKS

Status of the Claims

Before entry of the instant amendment, claims 1 to 43 are pending. In the instant amendment, claims 1 to 43 are canceled and new claims 44 to 87 are added.

Support for the Claim Amendment

The specification sets forth an extensive description of the invention in the new claims. Support for new claims directed to methods of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a non-immunogenic carrier, wherein the non-immunogenic soluble carrier has been subjected to a preparative sizing technique to remove substantially most high molecular weight non-immunogenic soluble carrier molecules before conjugation, or coupling, to two or more of the epitope molecules, is found, *inter alia*, at page 31, line 39 to page 32, line 9. Support for new claims directed to methods of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a non-immunogenic carrier, wherein soluble carrier has been subjected to a preparative sizing technique to remove substantially most high molecular weight immunogenic soluble carrier molecules after conjugation, or coupling, to two or more of the epitope molecules, is found, *inter alia*, at page 31, line 39 to page 32, line 9.

IDS and FORM PTO 1449

A copy of the Information Disclosure Statement and FORM PTO 1449 filed with the parent application is enclosed herewith.

Sequence Listing as required by 37 CFR §§1.821(c), 1.822 and 1.823

The application has been amended to insert SEQ ID NO:'s into the specification of the application. A RESPONSE TO NOTICE TO COMPLY WITH SEQUENCE RULES/ REQUEST FOR TRANSFER OF SEQUENCE INFORMATION is filed herewith.

Petition to Correct Inventorship under 37 CFR §1.48(b)

James K. Blodgett, John C. Cheronis, and Gary Kirschenheuter have been deleted as co-inventors; these individuals were co-inventors solely on claims pertaining to chemically-derivitized suppressing constructs (originally filed claims 20-23, 25, 33, 36, and 39-43) which, after entry of the instant amendment, will be no longer pending in the present application. A Petition to Correct Inventorship under 37 CFR §1.48(b) is being filed with this amendment.

CONCLUSION

In view of the foregoing remarks and the instant amendment, it is believed that the all claims pending in this application (after entry of the instant amendment) are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no fee is required for submission of this amendment. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 06-1050. Please credit any overpayments to the above-noted Deposit Account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Jan 08, 01

Gregory P. Einhorn
Reg. No. 38,440

Fish & Richardson P.C.
4350 La Jolla Village Drive, Suite 500
San Diego, CA 92122
Telephone: (858) 678-5070
Facsimile: (858) 678-5099

10078270.doc